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<b>(21) International Application Number:</b> PCT/US91/08993 <b>(22) International Filing Date:</b> 27 November 1991 (27.11.91) <b>(30) Priority data:</b> 618,395 27 November 1990 (27.11.90) US <b>(71) Applicant:</b> BIOLAB PHARMACEUTICALS, INC. [US/ US]; 50 Brigham Hill Road, Grafton, MA 01219 (US). <b>(72) Inventor:</b> PICHIERRI, Virgil, F. ; 50 Brigham Hill Road, Grafton, MA 01219 (US). <b>(74) Agent:</b> JUDSON, David, H.; Hughes & Luce, 1717 Main Street, Suite 2800, Dallas, TX 75201 (US).		<b>(81) Designated States:</b> AT (European patent), BE (European patent), BR, CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (Eu- ropean patent), IT (European patent), LU (European pa- tent), NL (European patent), SE (European patent).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> DIAPER RASH TREATMENT  <b>(57) Abstract</b>  An improved method of treating diaper rash in both infants and adults is described. The method entails coating the affect- ed area with a composition containing a copolymer of a lower alkyl vinyl ether and maleic acid, or a derivative of the copolymer.		

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### DIAPER RASH TREATMENT

Diaper rash is an inflammation of the skin in the diaper area of neonates, infants, children, and  
5 incontinent adults. It is generally believed caused by the metabolic by-products of both urine and feces. Currently available treatments for diaper rash are generally based upon the use of zinc oxide, vitamins (A, D, and D<sub>3</sub>), or some combination  
10 thereof. These active ingredients are incorporated into a cream or salve by blending them into various purified semisolid ointment bases, e.g. mineral oil, petrolatum, soft paraffin, lanolin, and the like. While these treatments are oftentimes effective for  
15 treating routine, simple diaper rashes, severe cases of diaper rash, especially those often observed with incontinent adults, have proved resistant to the treatments.

Accordingly, there is a need for an improved  
20 diaper rash treatment, particularly for use in severe cases.

The primary component of the compositions used herein for the improved treatment of diaper rash is a copolymer of a lower alkyl vinyl ether and maleic  
25 acid. U.S. Patent Nos. 3,003,988 and 4,393,080 disclose the use of the copolymer and derivatives thereof as an adhesive for fixing dentures or ostomy devices to mucous membranes. U.S. Patent No. 4,910,247 discloses a blend of a mixed salt of the  
30 copolymer in combination with a stearic acid metal salt as an improved adhesive for denture and ostomy use. U.S. Patent No. 3,876,771 discloses a skin protection gel for use in protecting a stoma from fecal matter and still active gastric juices, which  
35 gel contains 25 to 95% isopropanol along with the monoisopropyl ester of the copolymer. U.S. Patent

No. 4,007,263 discloses a method of relieving irritation of skin (due to fecal drainage) surrounding an iliac stoma by applying thereto a composition containing at least 40% of a calcium, sodium partial mixed salt of the copolymer in a petroleum jelly base. U.S. Patent No. 4,728,642 discloses a method of treating wounds by packing a wound emitting a large amount of fluid with granular material and then covering the wound site with an adhesive layer containing in part the copolymer or a derivative thereof. European Appln. 0,260,859 discloses a medicated skin composition containing the copolymer, isopropyl alcohol, citric acid ester plasticizer, and a specific antimicrobial agent.

Accordingly, the copolymer and its derivatives, while having been found to have utility as an adhesive, for protecting and relieving irritation from fecal matter (normally neutral or slightly alkaline) around a stoma, as part of an adhesive layer over a wound, and as a carrier/adhesive for an antimicrobial agent, has not been used as a treatment for diaper rash or to relieve skin irritation caused by contact with urine (normally slightly acidic), its metabolic by-products, infant feces (usually acidic), and its metabolic by-products.

It is thus an object of the present invention to produce a treatment for and inhibition of diaper rash in neonates, infants, children, and incontinent adults, which treatment is effective even in severe cases of diaper rash.

The present invention comprises treating a diaper rash in which urine and/or its metabolic by-products are the cause of or a contributing factor to the rash. More particularly, in one embodiment of the invention for the treatment of

severe diaper rash the invention entails applying to a situs of the severe diaper rash a composition comprising about 15 to 40% of a copolymer, or derivative thereof, of a lower alkyl vinyl ether and maleic acid dispersed in a semisolid ointment base, overcoating the copolymer composition with a layer of a semisolid water-insoluble ointment base, and allowing the copolymer composition to remain essentially intact for an extended period of time, generally through several diaper changes. Healing of the skin is generally observed within about 1 to 4 days. The overcoating layer is removed and then reapplied with each successive diaper change. Periodically, e.g. daily, the copolymer composition is removed (if it comes off easily) to inspect the skin and reapplied. In an alternative embodiment of the invention for the treatment of minor diaper rash as well as to inhibit the development of diaper rash, the invention entails applying at each diaper change a coating to the skin in the diaper area of a composition comprising about 5 to 20% of a copolymer, or a derivative thereof, of a lower alkyl vinyl ether and maleic acid dispersed in a semisolid ointment base.

The present diaper rash treatment utilizes a composition comprising a copolymer of a lower alkyl ( $C_1-C_3$ ) vinyl ether and maleic acid, or a derivative thereof, dispersed in a semisolid ointment base.

Suitable copolymers for use herein are commercially available from GAF Corporation, Wayne, New Jersey, and are currently sold under the trademark GANTREZ®. The copolymers are preferably used in the form of a derivative thereof in which one or both of the acid groups have been converted to a metal salt or an alkyl ester. Suitable metal salts include such as calcium, sodium, and a mixture

thereof. Suitable alkyl groups for the esters include propyl, isopropyl, butyl, isobutyl, and mixtures thereof. Generally about 20 to 90%, preferably about 70 to 90% for the metal salt and about 30 to 45% for the ester, of the initial carboxyl groups are reacted. The copolymers generally have a molecular weight of about 18,000 to 80,000 daltons (as measured by membrane osmometry in a 2-butanone 1-10 grams/1000 ml solution). The currently most preferred copolymer derivative is the mixed calcium and sodium salt blend supplied as GANTREZ® MS-955 wherein the proportion of Ca:Na is about 5-6:1 and the molecular weight is about 65,000 - 70,000. Other examples of specific copolymers useful herein include S-97 (intact acid groups), AN-169 (anhydride), ES-335 (monoisopropyl ester), ES-435 (monobutyl ester), and ES-425 (monobutyl ester).

The semisolid ointment base in which the copolymer is dispersed and which serves to prevent the copolymer from becoming too hard in use may be any such material conventionally used as a vehicle for medicinal substances for topical application. Suitable water-insoluble ointment bases for use herein include petrolatum, white petrolatum, lanolin, and the like. Suitable water-soluble ointment bases for use herein include polyethylene glycol polymers and the like. Preferably a water-insoluble ointment base is used because the water-soluble bases may in some instances be irritating to inflamed tissue as is present with a diaper rash.

Additional ingredients which may be present in the copolymer composition include oils such as mineral oil, fish liver oil, and cod liver oil; emollients such as glycerin, olive oil, and lanolin;

fillers such as cellulose gum, calcium carbonate, karaya gum, gum tragacanth, gum acacia, carboxymethyl cellulose, and polyvinyl acetate; vitamins such as vitamins A, D, and D<sub>3</sub>; astringents  
5 such as zinc oxide and aluminum acetate; protectants such as Peruvian balsam; coloring agents; odorants; and other materials which are conventionally used in relieving skin irritation.

Preferably the compositions used herein are  
10 alcohol-free since alcohol, which can be absorbed systemically, can be fatal to neonates and is likely to cause burning and be an irritant to previously irritated skin.

The viscosity of the compositions used herein  
15 has not been found to be critical, and thus the specific viscosity of the composition will be selected merely as a matter of convenience. Generally any conventional cream or ointment viscosity may be used with variations merely  
20 affecting the ease of application. Generally, however, compositions used for treatment of severe diaper rash will have a higher viscosity than those used for inhibiting and/or treating mild diaper rash.

Compositions particularly useful for treating  
25 severe cases of diaper rash, i.e. in which the skin is denuded, excoriated, ulcerated and/or severely inflamed, generally contain about 15 to about 40 weight percent of the copolymer, preferably about 20 to about 35 weight percent. The additional  
30 ingredients may be present in total amounts of up to about 50 weight percent, preferably up to about 30 weight percent. The balance of the composition is one or more semisolid ointment bases.

To utilize the compositions for severe diaper  
35 rash, they should be liberally applied over the specific irritation sites and then allowed to remain.

in place for an extended period of time, generally for several diaper changes. Healing generally has been noted to occur in about one to four days. To allow the treatment composition to remain in place for the extended period as well as to minimize any potential trauma and discomfort to the patient from repetitive removals of the composition and to prevent undue adherence to a diaper placed thereover, it has been found convenient to apply a coating of a semisolid water-insoluble ointment base, e.g. petrolatum or lanolin, atop the treatment composition. The ointment base top coating can then be removed for cleaning purposes and then reapplied for successive rediaperings while allowing the treatment composition to remain essentially undisturbed. Periodically, e.g. daily, the treatment composition should be removed to inspect the skin and additional composition applied if healing is not complete. During the periodic replacement of the treatment composition, if it does not readily detach from the skin it should be allowed to remain in place for an additional period to prevent trauma to the patient. When healing is complete, or earlier, the treatment composition may be completely removed by the conventional use of soap and water.

Compositions particularly useful for inhibiting the development of diaper rash and for treating mild cases thereof, i.e. in which the skin is slightly red, sore, warm to the touch, and/or the commencement of inflammation is evident, generally contain about 5 to 20 weight percent of the copolymer, preferably about 8 to 15 weight percent. The additional ingredients may then be present in amounts of up to about 60 weight percent, preferably up to about 40 weight percent. The balance of the composition is one or more semisolid ointment bases.

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To utilize the inhibiting and mild treatment compositions, they will generally be applied at a diaper change and then removed and reapplied at subsequent diaper changes in the same manner as other diaper rash products are currently utilized. If desired, an overcoating of a semisolid water-insoluble ointment base may be applied atop the treatment composition.

During use of the copolymer compositions it is currently believed that the copolymer component becomes at least partially hydrated which causes it both to adhere to the skin and to form a firmly adhered barrier against diaper rash causative and irritant agents. While diaper rash is believed caused primarily by the metabolic by-products of wastes in general, there are acidic components of urine and infant stools which are not present in adult feces and are particularly irritating. Urine consists of approximately 93-97% water and 3-7% solids which include urea, uric acid (20 to 40 gm/day), creatine (methylglycocyamine; 0 to 40 mg/day in men and 0 to 80 mg/day in women), creatinine (methylglycocyamidine; the end product of creatine metabolism; 15 to 25 mg/kg of body weight/day), ammonia (0.5 to 1.3 gm/ day), and inorganic substances such as chlorides, calcium, magnesium, and phosphorous. Urine is normally slightly acidic. Feces, on the other hand, of adults is normally neutral or slightly alkaline while that of infants is slightly acidic. It is the acidic agents which are believed to be highly irritating in the diaper area.

In the following non-limiting examples of diaper rash treating compositions and the use thereof, all parts and percents are by weight unless otherwise specified.

EXAMPLE I

An 8 month old congenital cardiac patient had had a continuing diaper rash for over 2 months. Various therapies, including antifungals were tried  
5 over this period without success.

Inspection of the skin indicated an underlying fungal infection as well as several areas of epidermal denudation. A single application of an antifungal powder, i.e. MYCOSTATIN, followed by a  
10 conventional skin sealant, i.e. Bard wipe, to hold the powder in place was applied to the perineum. A treatment composition was prepared by blending and uniformly mixing 30.75% GANTREZ® MS-955, 15.4% cellulose gum, 5% mineral oil, 0.0224% peppermint  
15 oil, 0.017% D+C Red #27 Lake, 0.01% D+C Red #30 Lake, and white petrolatum q.s.

The treatment composition was applied over the skin sealant and surrounding areas in an amount sufficient to form a coating about 1-2 mm thick. No  
20 pain or discomfort was experienced by the patient during the application of the treatment composition. The coating was then overcoated with a layer of petrolatum jelly and a diaper placed thereover. At each diaper change, only the white  
25 petrolatum overcoating was removed, the patient cleaned, and a fresh over-coating applied, i.e. the treatment composition remained intact.

Within two days, this chronic diaper rash had started to resolve. After 7 days no diaper rash  
30 inflammation was still visible and the treatment composition was removed by the liberal use of soap and water.

EXAMPLE II

The procedure of Example I was repeated with an  
35 8 month old ventilator dependent boy with medically managed Hirschsprungs disease who was bothered by

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occasional diarrhea. Several therapies had been tried without success when the treatment composition of Example I was directly applied to the diaper area of the patient, overcoated with a layer of petroleum jelly, and a diaper placed thereover. At each diaper change, only the white petrolatum overcoating was removed, the patient cleaned, and a fresh over-coating applied, i.e. the treatment composition remained intact.

Within only 24 hours considerable improvement of the diaper rash was readily apparent. After 2 days no diaper rash inflammation was still visible and the treatment composition was removed by the liberal use of soap and water.

EXAMPLE III

A 6 year old oncology patient developed intractable diarrhea during a course of chemotherapy. Both his energy level and mobility were diminished. His appetite was poor but he received optimal calories via parenteral nutrition. Because of his diminished level of activity he wore diapers. Despite preventative perianal care being administered using a protective moisture barrier cream of Carrington Company as well as numerous alternative conventional treatments and cleansing with each diaper change, severe perianal denudation occurred.

The perianal area was cleaned with a mild antibacterial soap and inspected for signs of underlying fungal infection. The skin appeared free from fungal infection. The treatment composition of Example I was applied to the denuded skin and covered with a layer of petroleum jelly as in Example I. Thereafter, each diaper change was performed by cleansing (while leaving the treatment composition intact) and reapplying the petroleum jelly.

Remarkable improvement in skin integrity was apparent after 24 hours and essentially complete healing was evident after 7 days.

### EXAMPLE IV

5 To inhibit the recurrence of the diaper rash on the patient of Example I, the following composition is applied and then removed on subsequent diaper changes: 10% GANTREZ® MS-955, 12% cellulose gum, 21% mineral oil, 10% lanolin, 3% zinc oxide, 0.0224%  
10 peppermint oil, and white petrolatum q.s. No recurrence is noted during a 20 day observation period.

### EXAMPLE V

The following compositions are prepared for  
15 treating severe diaper rash:

		Amount					
Ingredient		A	B	C	D	E	F
20	Gantrez@MS-955	25	-	-	10	15	20
	Gantrez@ S-97	-	35	-	-	15	-
	Gantrez@ES-335	-	-	30	-	-	7
	Gantrez@ES-435	-	-	-	20	-	8
	Mineral oil	-	-	5	2	-	1
	Cod liver oil	4	-	-	10	-	1
	Cellulose gum	-	12	10	8	18	4
25	Calcium carbonate	16	-	10	-	12	-
	Karaya gum	-	4	-	12	-	-
	Vitamin A	2	-	12	-	-	5
	Vitamin D	2	-	6	-	-	2
	Aluminum Acetate	-	7	-	5	-	-2
	Colorant	-	-	-	-	0.01	0.02
	Odorant	-	-	-	0.1	-	-
	White petrolatum	qs	-	qs	-	-	qs
	Lanolin	5	-	-	11	20	2
	Petrolatum	-	qs	-	qs	qs	-

30       The compositions are used as in Examples I-III  
for a variety of patients including neonates,  
infants, and adult incontinent. Similar results to  
those of the Examples are observed in each case.

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EXAMPLE IV

The following compositions are prepared for regular use to inhibit diaper rash formation and to treat minor cases thereof:

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	Ingredient	Amount					
		A	B	C	D	E	F
	Gantrez®MS-955	5	-	10	-	15	-
	Gantrez® S-97	2	4	-	7	3	10
	Gantrez®ES-335	-	1	6	-	-	-
10	Gantrez®ES-435	5	-	-	15	-	-
	Mineral oil	15	-	20	-	5	10
	Cod liver oil	7	10	-	-	15	-
	Cellulose gum	-	10	15	-	-	20
	Karaya gum	2	-	-	12	-	-
	Vitamin A	-	-	10	-	15	-
	Vitamin D	-	5	-	8	-	12
15	Aluminum Acetate	7	-	12	-	20	-
	Colorant	-	0.01	-	-	0.05	-
	Odorant	0.1	-	0.05	-	-	-
	White petrolatum	q.s.	-	q.s.	-	q.s.	-
	Lanolin	10	-	10	-	20	25
	Petrolatum	-	q.s.	-	q.s.	-	q.s.

The compositions are used by application of a fresh coating with each diaper change to a group of 10 neonates. A second group of 10 neonates, used as a control, are washed thoroughly at each diaper change. After 10 days, the untreated neonates exhibit substantially increased incidence of diaper rash.

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**CLAIMS:**

1. A method of treating a diaper rash which comprises:

applying to an area of diaper rash a  
5 composition containing about 15 to about 40% by weight of a copolymer of an alkyl vinyl ether having about 1 to 3 carbon atoms in the alkyl group and maleic acid, and derivatives thereof, the copolymer being dispersed in a topically-acceptable carrier;

10 over-coating the composition with a layer of semisolid ointment base; and

removing and reapplying the layer during successive diaper changes while allowing the composition underlying said layer to remain  
15 essentially undisturbed throughout said successive diaper changes to thereby enable the skin to heal.

2. The method of Claim 1, wherein the copolymer composition is removed after about one day  
20 and reapplied if healing is not complete.

3. The method of Claim 1, wherein about 20 to about 90% of acid groups of the maleic acid are reacted to convert them to a group selected from the  
25 group consisting of a metal salt and an alkyl ester having about 2 to 6 carbon atoms.

4. The method of Claim 3, wherein about 70 to 90% of the acid groups are converted to metal salts  
30 selected from the group consisting essentially of calcium, sodium, and mixtures thereof.

5. The method of Claim 3, wherein about 30 to 45% of the acid groups are converted to alkyl esters  
35 wherein the alkyl group is selected from the group consisting of propyl, isopropyl, butyl, isobutyl, and mixtures thereof.

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6. The method of Claim 1, wherein the topically-acceptable carrier is selected from the group consisting essentially of petrolatum, white petrolatum, and lanolin.

5

7. The method of Claim 2, wherein the over-coat layer is selected from the group consisting of petrolatum, white petrolatum, and lanolin.

10

8. The method of Claim 1, wherein the composition further contains at least one additive selected from the group consisting of oils, emollients, fillers, vitamins, astringents, coloring agents, and odorants.

15

9. The method of Claim 1, wherein the composition comprises about 20 to about 35% of the copolymer and derivatives thereof.

20

10. The method of Claim 1, wherein the composition is alcohol-free.

11. A method of inhibiting the formation of diaper rash and treating a mild case thereof which comprises (i) applying to the diaper area of a human selected from the group consisting of neonates, infants, children, and incontinent adults, a composition comprising about 5 to about 20% by weight of a copolymer of an alkyl vinyl ether having about 1 to 3 carbon atoms in the alkyl group and maleic acid and derivatives thereof dispersed in a semisolid ointment base, and (ii) removing the composition and reapplying additional composition at a subsequent diaper change.

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12. The method of Claim 11, wherein about 20 to about 90% of acid groups of the maleic acid are reacted to convert them to a group selected from the group consisting of a metal salt and an alkyl ester having about 2 to 6 carbon atoms.

13. The method of Claim 12, wherein about 70 to 90% of the acid groups are converted to metal salts selected from the group consisting essentially of calcium, sodium, and mixtures thereof.

14. The method of Claim 12, wherein about 30 to 45% of the acid groups are converted to alkyl esters wherein the alkyl group is selected from the group consisting of propyl, isopropyl, butyl, isobutyl, and mixtures thereof.

15. The method of Claim 11, wherein the semi-solid ointment base is selected from the group consisting essentially of petrolatum, white petrolatum, and lanolin.

16. The method of Claim 11, wherein the composition further contains at least one additive selected from the group consisting of oils, emollients, fillers, vitamins, astringents, coloring agents, and odorants.

17. The method of Claim 11, wherein the composition comprises about 8 to 15% of the copolymer and derivative thereof.

18. The method of Claim 11, wherein the composition is alcohol-free.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US91/08993

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC (5): A61K 31/74; A61F 13/15 U.S. CL. 424/78.08		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
U.S.	424/78.08; 514/865; 604/360	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>9</sup>		
Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X Y	US, A, 4,382,919 (ALONSO ET AL.) 10 MAY 1983 See entire document, especially column 3, line 48 - column 5, line 19.	11, 15-18 1-10, 12-14
Y	US, A, 3,876,771 (DENNER) 08 APRIL 1975; See column 2, lines 35-55; column 2, line 67 - column 3, line 9; column 4, lines 31-37.	3, 5, 12, 14
Y	US, A, 4,728,642 (PAWELCHAK ET AL.) 01 MARCH 1988 See column 3, lines 61-68.	3, 4, 12, 13
<p>* Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
12 February 1992		24 MAR 1992
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ISA/US		Donald R. McPhail

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